REMARKS

I. The Office Action

Claims 1-62 are currently pending in the application. Claims 30-36, 38, and 39 are under examination, and claims 1-29, 37, and 40-62 are withdrawn. In the Office Action, the examiner withdrew the rejections of claims 30-36, 38, and 39 under 35 U.S.C. § 112, second paragraph, and under 35 U.S.C. § 102(b) over either Kollet et al., *Blood*, 97(10):3283-91 (2001) or Kollet et al., *Exp. Hematol.*, 28(6):726-36 (2000). The examiner imposed a new rejection of claims 30-36, 38, and 39 under 35 U.S.C. § 103(a) as assertedly obvious over Kollet et al., *Blood*, 97(10):3283-91 (2001) (hereinafter "Kollet"), Heissig et al., *Cell*, 109(5):625-37 (2002) (hereinafter "Heissig"), Rafii et al., U.S. Patent Publication No. 2004/0071687 (hereinafter "Rafii"), Togawa et al., *Cancer Lett.*, 146(1):25-33 (1999) (hereinafter "Togawa"), and Sadatmansoori et al., *Protein Expr. Purif.*, 23(3):447-52 (2001) (hereinafter "Sadatmansoori").

II. The Rejections under 35 U.S.C. § 103(a) Should Be Withdrawn.

The Office's reasoning in support of the obviousness rejection appears to be that Kollet teaches that increased stromal derived factor-1 (SDF-1) levels lead to up-regulation of CXCR4, that Heissig teaches that increased levels of SDF-1 lead to up-regulation of the matrix metalloprotease MMP-9, and that Rafii teaches that MMP-9 promotes release of SDF-1. Thus, according to the Office, because MMP-9 promotes release of SDF-1 and SDF-1 leads to up-regulation of both MMP-9 and CXCR4, one of skill in the art would expect that MMP-9 would lead to up-regulation of CXCR4 via up-regulation of SDF-1. The Office's reasoning, however, is based on mischaracterizations of the references.

In regard to the teachings of Kollet, the Office stated that "pretreatment of cells with cytokines (e.g. SDF-1) lead to up-regulation of CXCR4 expression, which increased both in vitro migration to SDF-1 and in vivo homing." See Office Action, p. 8. The Office also stated that Heissig's teaching that MMP-9 increases bone marrow (BM) homing provided the molecular mechanism for the teaching of Kollet, which the Office characterized as the pretreatment of cells with SDF-1 leading to up-regulation of CXCR4.

Id., at p. 10. Kollet, however, did not teach that pretreatment of cells with SDF-1 leads to up-regulation of CXCR4 expression. Kollet et al. performed experiments to test the potential of human SDF-1 to attract stem cells *in vivo*. To that end, Kollet showed that injection of human SDF-1 into the BM of NOD/SCID mice increased the number of primitive $CD34^{+}CD38^{-/low}$ cells homing to the BM. See p. 3287. In the same paragraph, the authors describe pretreating $CD34^{+}$ or $CD34^{+}CD38^{-/low}$ cells with Stem Cell Factor (SCF) (not SDF-1). Pretreatment of the cells *in vitro* with SCF together with IL-6 (but not SDF-1) induced increased surface expression of CXCR4 and migration toward SDF-1. Moreover, the pretreatment with SCF and IL-6 occurred *in vitro* and was followed by injection of the pretreated cells into mice. Kollet did not demonstrate that pretreatment of cells with SDF-1 (rather than SCF and IL-6) led to up-regulation of CXCR4, increased migration to SDF-1, and *in vivo* homing, as the Office asserted. Instead, it was pretreatment with SCF and IL-6 that caused up-regulation of CXCR4 (the receptor for SDF-1), allowing increased BM homing of the stem cells to the SDF-1 gradient. Thus, the Office relied on a faulty premise to assert that Heissig taught the molecular mechanism of MMP-9-mediated induction as underlying Kollet's observations that pre-treatment of cells with SDF-1 leads to increased CXCR4.

The Office also mischaracterized the teachings of Rafii in stating that Rafii "teaches that MMP-9 promotes release of stem cell active cytokines (e.g. SDF-1), thereby promoting expansion of quiescent stem cells, and this novel concept lays the foundation of developing strategies where activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization." See Office Action, p. 11. This represents an exact quote of paragraph 114 of Rafii except for the addition of "(e.g. SDF-1)" by the Office. In fact, nowhere in Rafii is there a disclosure or suggestion of SDF-1 as a stem cell-active cytokine whose release is promoted by MMP-9. The Office goes on to use the above-quoted language as a basis to combine Heissig and Rafii to yield a combined teaching of a "functional positive feedback loop of increased SDF-1/CXCR4 interaction and increased MMP-9 expression in regulation of hematopoietic stem cells (HSCs) mobilization and differentiation." *Id.* No such positive feedback loop is disclosed or suggested by Rafii and/or Heissig because Rafii does not teach that MMP-9 promotes release of SDF-1. Both Rafii and

Heissig teach that increased levels of SDF-1 lead to up-regulation of MMP-9. See Rafii, paragraph 199; Heissig, p. 630, left column, last paragraph. The positive feedback loop proposed by the Office would lead to runaway expression of SDF-1 and MMP-9. In other words, an increase in MMP-9 would lead to an increase in SDF-1, which would lead to a further increase in MMP-9, in an ever-escalating spiral of mutually increased expression. None of the references cited by the examiner, alone or in combination, teach or suggest the positive feedback loop proposed by the Office. Thus, the Office improperly relied upon a flawed understanding of the cited references as a basis for combining the teachings of Rafii and Heissig to arrive at the conclusion that the claims would have been obvious.

To support a conclusion that a claim would have been obvious, the Office must show that all of the claimed elements were known or suggested in the cited references or in the state of the art, and that one of skill in the art would have combined the elements with no change in their respective functions. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). In no instance does Rafii or Heissig, alone or in combination, disclose or suggest that MMP-9 promotes release of SDF-1. The Office cited no reason to combine Rafii and Heissig in order to arrive at the use of matrix metalloprotease MMP-9 to induce expression of SDF-1, in turn leading to increased CXCR4 expression and HSC homing to BM. The cited references do not disclose, or even suggest, that exposing stem cells to an exogenous matrix metalloprotease allows one to isolate cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease, as required by claim 30. Moreover, the remaining cited references, Togawa and Sadatmansoori, do not remedy any of these defects and the Office has not contended otherwise. Thus, the Office has not provided a reason for combining the cited references and has not established that one of skill would have a reasonable expectation of successfully arriving at the claimed subject matter. Accordingly, the Office has not established a *prima facie* basis for rejecting any of the claims as obvious under 35 U.S.C. § 103(a) over Kollet in view of Heissig, Rafii, Togawa, and Sadatmansoori, and the rejection should be withdrawn.

III. Conclusion

In view of the above remarks, Applicants submit that the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

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Respectfully submitted,

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